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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,592	02/13/2004	Khue Vu Nguyen		5817

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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/777,592	NGUYEN, KHUE VU	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3 will be examined on the merits.

2. An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent Roster." Applicants may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313-1450.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

4. The abstract of the disclosure is objected to because it consists of four paragraphs instead of the required single paragraph. Correction is required. See MPEP § 608.01(b).

Claim Objections

5. Claims 1-3 are objected to because of the following informalities: There are several grammatical or spelling errors in the claims. For example, the word "denaturating" in claim 1 should read "denaturing". Each claim should be a continuous sentence punctuated by commas, semicolons and colons, with a period only at the end of each claim (see MPEP section 608.01(m)). Only the first word of the claim should be upper case. Appropriate correction is required.

The use of the trademarks/trade names such as PFASTBAC™ and DH10BAC™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. It is also noted that claims 2 and 3 contain the terms pBlueBacHis2A, INVαF' and pET-28a(+) which should also be identified properly since these are trademarks/trade names for vectors or competent cells. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Interpretation

6. Prior to examination of the claims, the claims must first be construed. Claim 2 refers to ligating the APP_{751}-cDNA and APP_{770}-cDNA fragments to the PFASTBAC™

HTb vectors and introducing the ligation products in INVαF' E. Coli strain. This will be interpreted as separate ligations into separate vectors for each fragment, not simultaneous ligation into the same vector molecule, since separate vectors are then selected which appear to each contain only one of the fragment sequences.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: cloning of the human APP gene. The method only recites reverse transcription followed by PCR with no additional steps related to the stated goal of the method, cloning the human SMN gene.

Claims 2 and 3 contain the trademark/trade names pFastBac™, DH10Bac™, and pCR®II. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods

themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a vector and competent cells, respectively, and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Games et al. (U.S. Patent No. 6,717,031) in view of Kang et al. GenBank Accession No. Y00264, (1993) and further in view of Powell (PCR Protocols: A Guide to Methods and Applications (1990) by Academic Press, Inc. pages 237-243) and further in view of Buck (Biotechniques (1999) 27(3): 528-36) and further in view of Innis et al. (PCR Protocols: A Guide to Methods and Applications (1990) by Academic Press, Inc. pages 3-12).

Games teaches a procedure for cloning human βA precursor protein gene (human APP gene including the 751 and 770 isoforms, column 37, lines 43-47) based on the reverse transcription (RT) and the polymerase chain reaction (PCR) using synthesized oligonucleotides for the reverse transcription and PCR steps (column 37, lines 34-41), comprising:

isolating RNA (column 37, lines 34-35); and

performing a one-step RT-PCR reaction using one of the synthesized oligonucleotide primers and performing the PCR reaction using the synthesized oligonucleotides as PCR primers (APP primers, column 37, lines 37-39) under the following conditions: denaturing at 94°C for 1 minute; annealing at 60°C for 40 seconds; and elongating at 72°C for 50 seconds (column 37, lines 40-41). The resulting fragments for APP isoforms 751 and 770 were then subcloned for sequencing (column 37, lines 43-47).

Games does not teach a separate RT step or the use of specific primers representing SEQ ID Nos. 1-3. Games also teaches slightly different PCR reaction conditions, such as annealing at 60°C for 40 seconds instead of 55°C for 2 minutes.

Kang teaches a sequence of the human βA precursor protein gene including sequences 100% homologous to SEQ ID No. 1 (positions 2367-2378), SEQ ID No. 2 (positions 148-164), and SEQ ID No. 3 (positions 2217-2235).

Powell teaches methods of RT-PCR, including separate cDNA synthesis and PCR steps (p. 240, line 28 to p. 241, line 16). Powell also teaches that reverse transcription may be performed using oligo-dT primers or a specific primer (page 243, lines 1-6). Powell further states, "One of the advantages of using specific primers close to the site of modification is that cDNA synthesis and subsequent amplification may be performed on less than intact preparations of total RNA" (page 243, lines 6-9).

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page

530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Innis teaches general conditions for PCR amplification. These conditions are: 25 to 35 cycles of 96°C for 15 seconds (usually with a longer initial denaturation step), 55°C for 30 seconds, and 72°C for 1.5 minutes (page 4). Innis expressly states, "It can be highly advantageous to optimize the PCR for a given application" (page 4). Innis further teaches on pages 7-9, that parameters such as the time and/or temperature of the denaturation, annealing, and extension steps, as well as the number of cycles should be optimized based on the specific properties (base composition, length, concentration) of the target and primer sequences.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to combine the teachings of Games, Kang, Powell, Buck and Innis. Games expressly teaches generation of RT-PCR products from the human βA precursor protein gene, including the 751 and 770 isoforms, and subcloning of these for sequence analysis. Since Powell taught that a specific reverse transcription primer permitted cDNA synthesis and subsequent amplification from less than intact RNA preparations (see above), the ordinary practitioner would have been motivated to substitute a specific RT primer for the one-step RT-PCR method of Games in order to promote more robust, accurate cDNA synthesis. Furthermore, since the human βA precursor protein gene sequence was known, as evidenced by Kang (cited above), and since Buck demonstrated the equivalence of different primer sequences (see above), the person of ordinary skill would have been motivated to select any desired specific reverse transcription and PCR amplification primers based on the known human βA precursor protein gene sequence to clone the gene, expecting a reasonable level of success.

Regarding the selection of particular primer sequences, attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art

compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties".

As noted above, the human βA precursor protein gene sequence was well known in the art at the time of invention, as evidenced by the GenBank deposit of Kang. Since the claimed primers simply represent structural homologues, which were derived from a sequence suggested by the prior art as useful for amplification primers, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Finally, since Innis taught that PCR amplification conditions should be optimized based on the base composition, length, and concentration of the target and primer sequences (see Innis, pages 4 and 7-9), the ordinary practitioner would have motivated to optimize the thermal cycling profile in order to maximize product yield without compromising reaction specificity. Attention is further directed to the court decision *In re Aller*, 105 USPQ 233 at 235:

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the claimed RT and PCR reaction conditions was other than routine or that the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, the person of ordinary skill in the art, interested in obtaining a human βA precursor protein gene product, would have been motivated to perform the RT-PCR method taught by Games using any primer set derived from the known human βA precursor protein gene sequence, as suggested by Powell, Kang, and Buck, under optimized reaction conditions, as suggested by Innis, thus resulting in the instantly claimed method.

11. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Essalmani et al. (FEBS Letters (1996) 389: 157-161) in view of the Invitrogen TOPO TA cloning manual, version N (copyright 1999-2001) and further in view of the Invitrogen Bac-to-Bac Baculovirus Expression System product information sheet (published 2002 by Invitrogen) and further in view of the Invitrogen pBlueBacHis2 A, B, and C product information sheet, version G (published Feb. 7, 2003), and further in view of the 1997 Invitrogen catalog (published 1997, page 85) and further in view of Sambrook et al. (Molecular cloning: a laboratory manual (1989) by Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, pages 1.53-1.61).

Essalmani teaches construction of vectors (pAcCL29) containing the human amyloid precursor protein gene (APP) from cDNA containing the APP695 gene and expression of the gene and cotransfection of insect cells with the plasmid and linear viral DNA to obtain recombinant baculoviruses for reinfection of insect cells for expression of the gene (p. 157, column 2, lines 16-27).

Essalmani does not teach transfer of the APP gene from a pCR®II vector to a pFastBac vector followed by transformation into INVαF' and DH10Bac cells, colony screening and sequencing.

The Invitrogen Bac-to-Bac Baculovirus Expression System product information teaches that this expression system offers: "(a) tremendous time savings over traditional baculovirus methods, (b) high-level recombinant protein yields, (c) easy cloning (see page 1)." This product information sheet teaches that the pFastBac™ vector offers "high-level, native protein expression and a large multiple cloning site for simplified cloning" (page 3). This product information sheet further teaches that the multiple cloning site has XbaI and HindIII sites (see Figure 4). Finally, the product information sheet teaches transformation of the recombinant pFastBacTM construct into DH10Bac competent E. coli followed by blue-white screening for inserts (see page 5 and Figure 6).

This product information sheet does not teach screening in INVαF' cells or generating an expression construct using the pBlueBacHis2 A™ vector. Also, this product information sheet does not teach that the construct is generated by digesting the gene of interest from the pCR®II vector.

The Invitrogen pBlueBacHis2 A, B, and C product information sheet teaches that these baculovirus transfer vectors are designed for expression and purification of recombinant proteins in insect cells (page 1). This product information sheet states, "The histidine residues create a high-affinity metal binding site to allow purification of recombinant fusion proteins on nickel-chelating resin" (page 1). This reference teaches

that the pBlueBacHis2 A vector has a HindIII site and NcoI site in the multiple cloning site (see page 3), and further teaches that the vector has blue-white screening capabilities (see Appendix, page 11).

Similar to the previous reference, this product information sheet does not provide specific details of the method of transferring a gene in a pFastBac™ vector to the pBlueBacHis2 A vector, such as alkaline phosphatase treatment or use of a specific cloning vector (pCR®II). Rather, the user is directed to Sambrook et al. (Molecular cloning: a laboratory manual, 1989) or other similar references for guidance (see page 2). Also, although this reference recommends transformation into a recA and endonuclease A deficient strain and provides several examples of suitable bacterial strains, INVαF' cells are not explicitly taught (page 2).

The 1997 Invitrogen catalog (page 85) teaches INVαF' competent E. coli cells. This strain is recA and endonuclease A deficient. Invitrogen teaches that these cells "are ideal for propagating plasmids and cDNA library construction. They allow stable replication of high-copy plasmids" (page 85). The genotype offers the following features: (a) blue-white screening, (b) reduction of homologous recombination of transformed plasmids (recA), and (c) increased quality of plasmid DNA preparations (endA1) (see page 85).

The Invitrogen TOPO TA cloning manual (published 2001) teaches that the pCR®II-TOPO vector provides "a highly efficient, 5 minute, one-step cloning strategy for the direct insertion of Taq polymerase PCR amplified products into a plasmid vector. No ligase, post-PCR procedures, or PCR primers containing specific sequences are

required" (page 1). This vector contains HindIII and XbaI sites in the cloning site (see page 10).

Sambrook teaches a general protocol for cloning in plasmid vectors. Sambrook teaches that genes may be transferred between different vectors (such as a cloning and expression vector) via restriction enzyme digestion to release the fragment of interest followed by ligation into the new vector and transformation into competent E. coli (page 1.53-1.54; see also Figure 1.6). Sambrook teaches that digestion with two different restriction enzymes is desirable, because the background of nonrecombinant clones is low and the insert is only capable of ligation in one orientation (see Table 1.2). Sambrook teaches that the vector must also be digested using the same restriction enzymes used to release the insert, followed by alkaline phosphatase treatment to prevent re-circularization of the vector (see Figure 1.8 and pages 1.60-1.61, where calf intestinal alkaline phosphatase is taught).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to construct expression plasmids of the human APP gene in either the FastBac or BlueBacHis2A expression vectors according to the claimed procedure. Essalmani taught expression constructs of the human APP gene using a variety of plasmid vector construct and coinfection of insect cells to produce baculovirus vectors (p. 389, column 2, lines 16-27, see above), but did not specify a preferred baculovirus expression vector system. As discussed above, the FastBac and BlueBacHis2A systems offered the user rapid, stable expression of recombinant proteins. The BlueBacHis2A system further afforded the ability to rapidly and efficiently purify the

expressed protein using a histidine affinity tag (see above product information sheet). The ordinary practitioner would have been motivated to generate APP expression constructs as suggested by Essalmani using the baculovirus vectors taught by Invitrogen in order to rapidly produce a high yield of recombinant protein, capable of being purified using simple, often one-step affinity-based methods. Since the Invitrogen product information sheets provided specific guidance as to the method of producing the expression construct, and Sambrook taught specific details of molecular cloning, the ordinary practitioner would have expected a reasonable level of success in producing the claimed expression constructs. Finally, regarding the choice of cloning host cells, the Invitrogen product information sheet for pBlueBacHis2A taught that the major requirement for the host cell is a strain deficient in recA and endA activity, and further taught that in addition to the exemplary E. coli strains mentioned on page 2, other equivalent strains could be used. Since the Invitrogen catalog taught that INVαF' cells were recA and endA deficient and useful for routine cloning applications (see above), the ordinary practitioner would have been motivated to substitute any suitable recA endA deficient cell line in the method. In short, the claimed method is directed to obtaining an expression construct of a known gene (APP) in a known expression system (FastBac or BlueBacHis2A) using well-known, standard methods, and therefore is prima facie obvious in light of the prior art teachings cited above.

12. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Essalmani et al. (FEBS Letters (1996) 389: 157-161) in view of the Novagen pET system manual (published February 1999) and further in view of Novagen catalog No.

TB074 (December, 1998) and further in view of the 1997 Invitrogen catalog (published 1997, page 85).

Essalmani teaches construction of plasmid vectors (pAcCL29) containing the human amyloid precursor protein gene (APP) from cDNA containing the APP695 gene and expression of the gene and cotransfection of insect cells with the plasmid and linear viral DNA to obtain recombinant baculoviruses for reinfection of insect cells for expression of the gene (p. 157, column 2, lines 16-27).

Essalmani does not teach an expression plasmid system using the pET-28a(+) bacterial expression vector. Essalmani also does not teach transfer the APP gene from the pFastBac vector followed by transformation into INVαF' cells and colony screening.

The pET system is a bacterial expression system developed by Novagen. The pET system manual states, "The pET system is the most powerful system yet developed for the cloning and expression of recombinant proteins in E. coli. Target genes are cloned in pET plasmids under control of strong bacteriophage T7 transcription and (optionally) translation signals; expression is induced by providing a source of T7 RNA polymerase in the host cell. T7 RNA polymerase is so selective and active that almost all of the cell's resources are converted to target gene expression; the desired product can comprise more than 50% of the total cell protein a few hours after induction. Another important benefit of this system is its ability to maintain target genes transcriptionally silent in the uninduced state. Target genes are initially cloned using hosts that do not contain the T7 RNA polymerase gene, thus eliminating plasmid instability due to the production of proteins potentially toxic to the host cell....Two types

of T7 promoter and several hosts that differ in their stringency of suppressing basal expression levels are available, providing great flexibility and the ability to optimize the expression of a wide variety of target genes" (page 3). The manual further teaches that the pET-28a(+) vector contains an N-terminal histidine tag for simple affinity purification of the recombinant protein (see Table on page 6).

Regarding preparation of a pET expression construct the manual presents the following procedure (see page 15 for a flowchart and specific recommendations on pages 18-26):

(a) prepare the pET vector by restriction enzyme digestion and dephosphorylation (step 1 on page 15; see also pages 18-19, where more details of the restriction enzyme digestion are presented and calf intestinal alkaline phosphatase is used to dephosphorylate the vector)

(b) prepare the insert DNA by restriction digestion (step 2 on page 15; see also page 19 for specific details of the digestion and isolation of the digested fragment)

(c) ligation of the insert and vector followed by transformation into the appropriate host (step 3 on page 15; see also pages 20-22 for specific details of the ligation and transformation)

(d) identify positive clones by colony PCR, miniprep, sequencing or in vitro transcription/translation (step 4 on page 15; see also pages 22-26 for specific details)

The manual teaches that suitable hosts for cloning include the following recA and endA deficient strains: NovaBlue, JM109, and DH5a (page 8), but does not teach the

INVαF' strain. Also the pET system manual does not teach digestion using the HindIII and SalI restriction enzymes.

Novagen catalog No. TB074 teaches the vector map of the pET-28a(+) vector. This vector contains HindIII and SalI sites in the cloning region (see page 1).

The 1997 Invitrogen catalog (page 85) teaches INVαF' competent E. coli cells. This strain is recA and endonuclease A deficient. Invitrogen teaches that these cells "are ideal for propagating plasmids and cDNA library construction. They allow stable replication of high-copy plasmids" (page 85). The genotype offers the following features: (a) blue-white screening, (b) reduction of homologous recombination of transformed plasmids (recA), and (c) increased quality of plasmid DNA preparations (endA1) (see page 85).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to construct expression plasmids of the human SMN gene in the pET-28a(+) expression system. Essalmani taught expression constructs of the human APP gene using a baculovirus vector system, as well as bacterial plasmid vectors (p. 389, column 2, lines 16-27, cited above), but did not specify a preferred bacterial expression vector system. As discussed above, the pET system offered rapid, stable, high-yield expression of recombinant proteins modified with a histidine tag for simple affinity purification (see above citation). The ordinary practitioner would have been motivated to generate APP expression constructs as suggested by Essalmani using the pET-28a(+) vector taught by Novagen in order to rapidly produce a large amount of recombinant protein, suitable for simple, often one-step affinity-based purification.

Since the Novagen product information sheets provided specific guidance as to the method of producing the expression construct (see above), and the vector map taught that the HindIII and SalI sites were available in the cloning site, the ordinary practitioner would have expected a reasonable level of success in producing the claimed expression constructs. Regarding the choice of cloning host cells, the Novagen pET system manual expressly taught that the major requirement for the host cell is a strain deficient in recA and endA activity, and further taught that in addition to the exemplary E. coli strains mentioned on page 8, other equivalent strains could be used. Since the Invitrogen catalog taught that INVαF' cells were recA and endA deficient and useful for routine cloning applications (see above), the ordinary practitioner would have been motivated to substitute any suitable recA endA deficient cell line in the method. In short, the claimed method is directed to obtaining an expression construct of a known gene (APP) in a known expression system (pET) using well-known, standard methods, and therefore is prima facie obvious in light of the prior art teachings cited above.

Conclusion

13. Claims 1-3 are rejected. No claims are allowable.

Correspondence

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas 9/12/06

David C. Thomas
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
9/11/06